4837

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :
C07C 69/738, 69/732, 59/90
C07C 59/56, 59/34
C07D 309/30, A61K 31/365
A61K 31/22, 31/19

A1

(11) International Publication Number: WO 86/ 03488

(43) International Publication Date: 19 June 1986 (19.06.86)

(21) International Application Number: PCT/EP85/00653

(22) International Filing Date: 29 November 1985 (29.11.85)

(31) Priority Application Number: 677,917

(32) Priority Date: 4 December 1984 (04.12.84)

(33) Priority Country: US

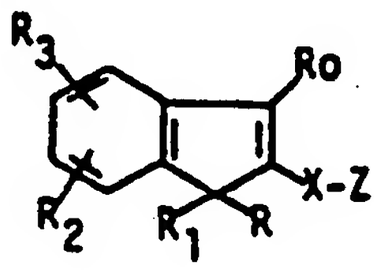
(71) Applicant: SANDOZ AG [CH/CH]; Lichtstrasse 35, CH-4002 Basel (CH).

(72) Inventors: KATHAWALA, Faizulla, G. ; 39 Woodland Avenue, Mountain Lakes, NJ 07946 (US). WATTANASIN, Sompong ; 39 3A Eagle Rock Village, Budd Lake, NJ 07828 (US).

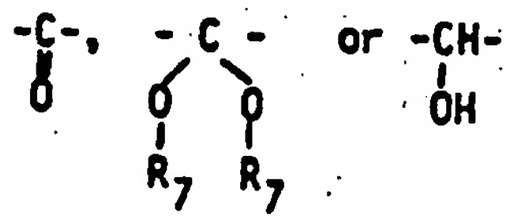
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

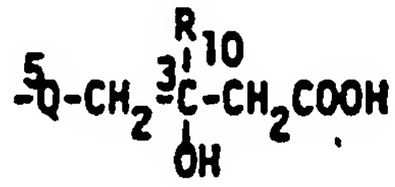
(54) Title: INDENE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF



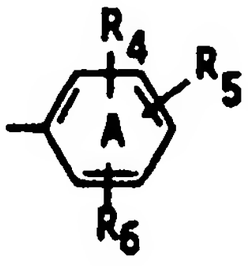
(I)



(IV)



(III)



(II)

(V)

(57) Abstract

Compounds of formula (I), wherein R is hydrogen or primary or secondary C_{1-6}alkyl, R_1 is primary or secondary C_{1-6}alkyl or R and R_1 together are $(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2- wherein m is 2, 3, 4, 5 or 6, Ro is C_{1-6}alkyl, C_{3-7}cycloalkyl or ring A (II) each or R_2 and R_4 is independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, each of R_3 and R_5 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy on each of the phenyl and indene rings X is -$(CH_2)_n$- or -$(CH_2)_q$CH=CH$(CH_2)_q$- wherein n is 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1, and Z is (III) wherein Q is (IV) wherein each R_7 is the same primary or secondary C_{1-6}alkyl or together they represent -$(CH_2)_2$-, -$(CH_2)_3$-, R_{10} is hydrogen or C_{1-3}alkyl, with the proviso that Q may be other than (V) only when X is -CH=CH- or -CH_2-CH=CH- and/or R_{10} is C_{1-3}alkyl, in free acid form, or in the form of an ester or -lactone thereof or in salt form as appropriate, which are indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

FOR THE PURPOSES OF INFORMATION ONLY

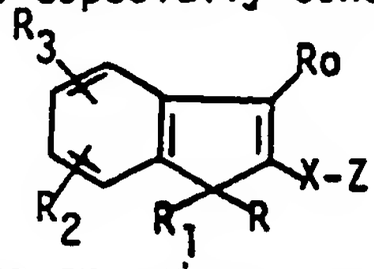
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BG	Bulgaria
BR	Brazil
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany, Federal Republic of
DK	Denmark
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
RO	Romania
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

INDENE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

The invention concerns indene analogs of mevalonolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as hypolipoproteinemic and anti-atherosclerotic agents.

The invention is especially concerned with compounds of formula I



I

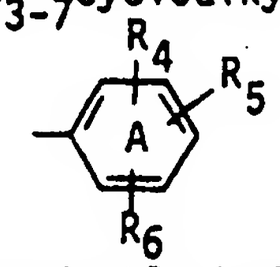
wherein R is hydrogen or primary or secondary C_{1-6}alkyl,

R_1 is primary or secondary C_{1-6}alkyl or

R and R_1 together are $(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2-

wherein m is 2, 3, 4, 5 or 6,

Ro is C_{1-6}alkyl, C_{3-7}cycloalkyl or ring A



each of R_2 and R_4 is independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

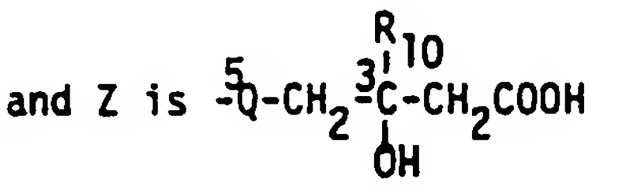
each of R_3 and R_5 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

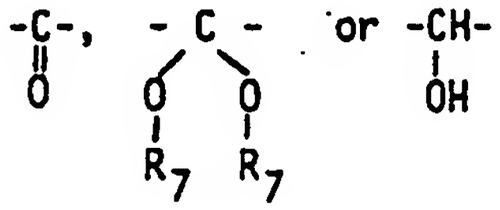
with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy on each of the phenyl and indene rings

X is $-(CH_2)_n-$ or $-(CH_2)_qCH=CH(CH_2)_q-$

wherein n is 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1,

and Z is 

II

wherein Q is 

wherein each R_7 is the same primary or secondary C_{1-6}alkyl or together they represent $-(CH_2)_2-$, $-(CH_2)_3-$,

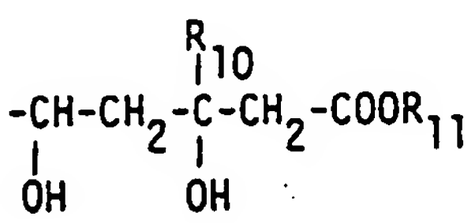
R_{10} is hydrogen or C_{1-3}alkyl,

with the proviso that Q may be other than $-\underset{\underset{OH}{|}}{CH}-$ only when X is -CH=CH- or $-CH_2-CH=CH-$ and/or R_{10} is C_{1-3}alkyl,

in free acid form, or in the form of an ester or -lactone thereof or in salt form as appropriate.

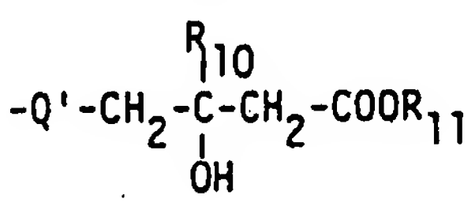
Suitable esters include physiologically acceptable esters e.g. physiologically hydrolysable and -acceptable esters.

By the term "physiologically-hydrolysable and -acceptable ester" is meant an ester of a compound in accordance with the invention in which the carboxyl moiety if present is esterified, and which is hydrolysable under physiological conditions to yield an alcohol which is itself physiologically acceptable, e.g. non-toxic at desired dosage levels. For the avoidance of doubt, throughout this application it is the right hand side of the X radical that is attached to the Z group. Preferred such esters as Z can be represented together with the free acid by formula IIa



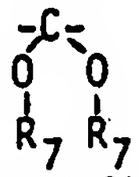
IIa

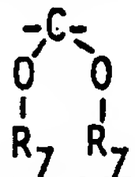
or formula IIc



IIc

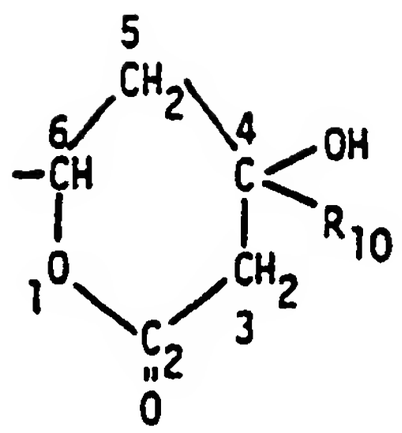
wherein R_{11} is hydrogen, C_{1-4}alkyl or benzyl preferably hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl,

Q' is $-\overset{\overset{O}{\|}}{C}-$ or  and

R_7 and R_{10} are as defined above with the further proviso that R_{11} is other than hydrogen when Q' is 

When IIa is in salt form R_{11} represents a cation.

When Z is in lactone form it forms a δ-lactone of formula IIb



IIb

and references to "lactone" hereinafter refer to δ-lactones.

Salts of the compounds of the invention, e.g. of the compounds of formula I, include in particular their pharmaceutically acceptable salts. Such pharmaceutically acceptable salts include e.g. alkali metal salts such as the sodium and potassium salts and salts with ammonium.

References to compounds of formula I, II, IIa, IIb and IIc and sub-species thereof are intended to cover all forms unless otherwise stated.

Depending on the nature of R_1 and R the compounds of formula I may be divided into two main groups, namely, those wherein R is hydrogen or primary or secondary C_{1-6}alkyl (Group IA) and those wherein R_1 and R together represent $-(CH_2)_m-$ or (Z)-CH_2-CH=CH-CH_2- (Group IB). These groups may be further divided depending on the nature of Z, namely when Q is $-\underset{OH}{CH}-$ and the Z is in other than lactone form (sub-group "a"); when Z is a group of formula IIb (sub-group "b"); and when Q is $-\overset{O}{\overset{\|}{C}}-$ or $-C\begin{matrix}O-R_7\\O-R_7\end{matrix}$ and Z is in other than lactone form (sub-group "c").

The resulting six groups are designated as IAa, IAb, IAc, IBa, IBb, IBc.

As is self-evident to those in the art, each compound of Groups IAa, IAb, IBa and IBb (and every subscope and species thereof) has two centres of asymmetry (the two carbon atoms bearing the hydroxy groups in the group of formula IIa and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of formula IIb and, therefore, there are four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers), provided that R and R_1 are identical or taken together are $-(CH_2)_m-$ or (Z)-CH_2-CH=CH-CH_2- and that R_{11} does not contain any centre of asymmetry. The four stereoisomers may be designated as the R,R, R,S, S,R and S,S enantiomers, all four stereoisomers being within the scope of this invention. When R and R_1 are different and/or R_{11} contains one or more centres of asymmetry, there are eight or more stereoisomers.

Since it is preferred that R and R_1 be identical or taken together $-(CH_2)_m-$ or (Z)-CH_2-CH=CH-CH_2- and that R_{11} does not contain a centre of asymmetry and for reasons of simplicity any additional stereoisomers resulting from the presence of a centre of asymmetry in the 1-position of the indene ring and/or one or more centres of asymmetry in R_{11} will usually be ignored, it being assumed that R and R_1 are identical or taken together are $-(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2- and that R_{11} is free of centres of asymmetry. As is also self-evident each compound of Groups IAc and IBc (and every subscope and species thereof) has one centre of asymmetry (the carbon atom bearing the hydroxy group in formula IIc and therefore there are two enantiomers of each compound, provided that R and R_1 are identical or taken together are $-(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2- and that R_{11} does not contain any centre of asymmetry. The two stereoisomers may be designated as the 3R and 3S isomers, both being within the scope of this invention. When R and R_1 are different and/or R_{11} contains one or more centres of asymmetry, there are four or more stereoisomers. For the reasons set forth above, any additional stereoisomers resulting from the presence of a centre of asymmetry in the 1-position of the indene ring and/or one or more centres of asymmetry in R_{11} will usually be ignored.

Ro preferably does not contain an asymmetric carbon atom and is preferably Ro' where Ro' is C_{1-4}alkyl not containing an asymmetric carbon atom or Ring A, more preferably Ro", wherein Ro" is ring A wherein R_4 is R_4', R_5 is R_5', and R_6 is R_6' even more preferably Ro"' where Ro"' is ring A wherein R_4 is R_4", R_5 is R_5" and R_6 is R_6" and most preferably Ro"" wherein Ro"" is ring A wherein R_4 is R_4"', R_5 is R_5"' and R_6 is R_6"'. In Ro"" R_4"' is preferably R_4"".

When R is hydrogen or primary or secondary C_{1-6}alkyl it is preferably hydrogen or primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom and is preferably R', where R' is hydrogen or primary or secondary C_{1-4}-alkyl not containing an asymmetric carbon atom, more preferably R" where R" is hydrogen or C_{1-2}alkyl and most preferably C_{1-2}alkyl and R_1 is preferably primary or secondary C_{1-6}alkyl not containing any asymmetric carbon atom and is preferably R_1', where R_1' is primary or secondary C_{1-4}alkyl not containing an asymmetric carbon atom, more preferably R_1", where R_1" is C_{1-3}-alkyl, and most preferably C_{1-2}alkyl.

Prferably, when R, R', etc. is other than hydrogen, R, R', etc., as the case may be, is identical to R_1, R_1', etc., as the case may be.

When R and R_1 taken together are $-(CH_2)_m-$ or (Z)-CH_2-CH=CH-CH_2-, they are preferably $-(CH_2)_m-$, more preferably $-(CH_2)_{m'}-$, even more preferably $-(CH_2)_{m''}-$ and most preferably $-(CH_2)_{m'''}-$, especially $-(CH_2)_4-$, wherein m is as defined above, and m', m" and m"' are as defined below.

R_2 is preferably hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}-alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy and is preferably R_2', where R_2' is hydrogen, C_{1-3}alkyl, methoxy, fluoro, chloro or benzyloxy, more preferably R_2", where R_2" is hydrogen or C_{1-3}alkyl, and most preferably hydrogen.

R_3 is preferably R_3', where R_3' is hydrogen or C_{1-3}alkyl, and more preferably hydrogen.

Preferably, not more than one of R_2 and R_3 is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy. More preferably, R_2 and R_3 are not ortho to each other unless at least one of them is a member of the group consisting of hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro and chloro.

R_4 is preferably hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}-alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy and is preferably R_4', where R_4' is hydrogen, C_{1-3}alkyl, trifluoromethyl, fluoro or chloro, more preferably R_4", where R_4" is hydrogen or C_{1-2}-alkyl, and most preferably R_4"', where R_4"' is hydrogen or methyl, especially R_4"", where R_4"" is hydrogen or 3-methyl.

R_5 is preferably R_5', where R_5' is hydrogen, C_{1-2}alkyl, fluoro or chloro, more preferably R_5", where R_5" is hydrogen or fluoro, and most preferably R_5'", where R_5'" is hydrogen or 4-fluoro.

R_6 is preferably R_6', where R_6' is hydrogen or C_{1-2}alkyl, more preferably R_6", where R_6" is hydrogen or methyl, and most preferably R_6"', where R_6"' is hydrogen or 5-methyl.

Preferably, not more than one of R_4 and R_5 is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy. More preferably no two of R_4 (R_4', R_4", etc.), R_5 (R_5', R_5", etc.) and R_6 (R_6', R_6", etc.) are ortho to each other unless at least one member of each pair of substituents that are ortho to each other is a member of the group consisting of hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro and chloro.

The preferred R_4-bearing phenyl groups are phenyl, 4-fluorophenyl, 3,4- and 3,5-dimethylphenyl, 4-fluoro-3-methylphenyl and 3,5-dimethyl-4-fluorophenyl, with 4-fluorophenyl and 3,5-dimethylphenyl being more preferred.

Preferably each R_7 is C_{1-3}alkyl or both R_7's taken together are $(CH_2)_2$ or $(CH_2)_3$; more preferably each R_7 is C_{1-2}alkyl or both R_7's taken together are $(CH_2)_2$ or $(CH_2)_3$ and most preferably each R_7 is C_{1-2}alkyl.

R_{10} is preferably R_{10}', where R_{10}' is hydrogen or methyl, and more preferably hydrogen.

R_{11} is preferably R_{11}', where R_{11}' is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl especially R_{11}'' where R_{11}'' is hydrogen or C_{1-3}-alkyl, more preferably R_{11}''' which is hydrogen or C_{1-2}alkyl.

Compounds of formula I wherein Z is of formula II, IIa or IIc are most preferably in salt form. Preferred salt-forming cations are those free from centres of asymmetry especially e.g. sodium, potassium or ammonium, most preferably sodium. Such cations may also be di- or tri-valent and are balanced by 2 or 3 carboxylate containing anions. Any -CH=CH- containing bridge as X is preferably trans i.e. (E).

X is preferably X' which is CH_2CH_2 or -(E)-CH=CH-, more preferably -(E)-CH=CH-.

Z is preferably a group of formula IIa, IIb or IIc wherein R_{10} is R_{10}' (especially hydrogen) more preferably a group of formula IIa, IIb or IIc, wherein R_{10} is hydrogen and R_{11} is R_{11}' or a cation even more preferably a group of formula IIa or IIb whereinR_{10} is hydrogen, and R_{11} is R_{11}'' or a cation;and most preferably a group of formula IIa wherein R_{10} is hydrogen, and R_{11} is a cation, especially sodium.

m is preferably m', where m' is 2, 3, 4 or 5, more preferably m", where m" is 2, 3 or 4, and most preferably m"', where m"' is 2 or 4, especially-4.

n is preferably 2.

As between otherwise identical compounds of formula I, those wherein Z is other than lactone form are generally preferred over those wherein Z is a group of formula IIb, with those wherein Q is CH being generally preferred over those wherein Q has another meaning.

Insofar as the compounds of Groups IAa and IBa and each of the subgroups thereof are concerned, the erythro isomers are preferred over the threo isomers, erythro and threo referring to the relative positions of the hydroxy groups in the 3- and 5-positions of the group of formula IIa.

Insofar as the compounds of Groups IAb and IBb and each of the subgroups thereof are concerned, the trans lactones are generally preferred over the cis lactones, cis and trans referring to the relative positions of R_{10} and the hydrogen atom in the 6-position of the group of formula IIb.

The preferred stereoisomers of the compounds of formula I having only two centres of asymmetry wherein X is -CH=CH- or $-CH_2-CH=CH-$ and Z is a group of formula IIa are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e. the 3R,5S-3S,5R (erythro) and 3R,5R-3S,5S (threo) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centres of asymmetry wherein X is $-(CH_2)_n-$ or $-CH=CH-CH_2-$ and Z is a group of formula IIa are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, i.e. the 3R,5R-3S,5S (erythro) and 3R,5S-3S,5R (threo) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and the 3R,5R isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centres of asymmetry wherein X is -CH=CH- or $-CH_2CH=CH-$ and Z is a group of formula IIb are the 4R,6S and 4R,6R isomers and the racemate of which each is a constituent, i.e. the 4R,6S-4S,6R (trans lactone) and 4R,6R-4S,6S (cis lactone) racemates, with the 4R,6S isomer and the racemate of which it is a constituent being more preferred and the 4R,6S isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centres of asymmetry wherein X is $-(CH_2)_n-$ or $-CH=CH-CH_2$, and Z is a group of formula IIb are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, i.e. the 4R,6R-4S,6S (trans lactone) and 4R,6S-4S,6R (cis lactone) racemates, with the 4R,6R isomer and the racemate of which it is a constituent being more preferred and the 4R,6R isomer being most preferred.

The preferences set forth in the preceding four paragraphs also apply to the compounds of Groups IAa, IAb, IBa, IBb having more than two centres of asymmetry and represent the preferred configurations of the indicated positions.

The preferred stereoisomers of the compounds of formula I having just one centre of asymmetry wherein Q is other than $\overset{|}{\underset{OH}{-CH-}}$ are the 3R isomers and the racemate of which they are constituents i.e. the 3R-3S racemate with the 3R isomer being more preferred. These preferences also apply to the compounds of Groups IAc and IBc having more than one centre of asymmetry and represent the preferred configuration of the indicated position.

Each of the preferences set forth above applies, not only to the compounds of formula I, but also to the compounds of Groups IAa, IAb, IAc, IBa, IBb and IBc as well as to every subgroup thereof set forth in the specification, e.g. Groups (i) et seq., unless otherwise indicated. When any preference contains a variable, the preferred significances of that variable apply to the preference in question, unless otherwise indicated.

Preferred groups of compounds of formula I include the compounds

(i) of Group IAa wherein Ro is Ro', R is R', R_1 is R_1', R_2 is R_2', R_3 is R_3', R_{10} is R_{10}', R_{11} is R_{11}' and X is X',

(ii) of (i) wherein Ro is Ro", R_{10} is hydrogen, R_{11} is $R_{11}"$, and X is (E)-CH=CH-,

(iii) of (ii) wherein Ro is Ro"', R is R", R_1 is $R_1"$, R_2 is $R_2"$, R_3 is hydrogen, and R_{11} is $R_{11}"'$, or especially a cation,

(iv) of (iii) wherein Ro is Ro"' wherein $R_4"'$ is $R_4""$, R is C_{1-2}alkyl, R_1 is C_{1-2}alkyl and R_2 is hydrogen

(v) of (iv) wherein R_{11} is a cation especially sodium, potassium or ammonium, especially sodium,

(vi) of Group IAb wherein Ro is Ro', R is R', R_1 is R_1', R_2 is R_2', R_3 is R_3', R_{10} is R_{10}', and X is X',

(vii) and (vi) wherein Ro is Ro", R_{10} is hydrogen, and X is (E)-CH=CH-,

(viii) of (vii) wherein Ro is Ro"', R is R", R_1 is $R_1"$, R_2 is $R_2"$ and R_3 is hydrogen,

(ix) of (viii) wherein Ro is Ro"" wherein $R_4"'$ is $R_4""$, R is C_{1-2}alkyl, R_1 is C_{1-2}alkyl and R_2 is hydrogen,

(x) of Group IBa wherein Ro is Ro', R and R_1 taken together are $-(CH_2)_m-$, R_2 is R_2', R_3 is R_3', R_{10} is R_{10}', R_{11} is R_{11}', and X is X',

(xi) of (x) wherein Ro is Ro", R_{10} is hydrogen, R_{11} is $R_{11}"$, and X is (E)-CH=CH-,

(xii) of (xi) wherein Ro is Ro"', R_2 is $R_2"$, R_3 is hydrogen, R_{11} is $R_{11}"'$, particularly a cation, and m is m',

(xiii) of (xii) wherein Ro is Ro"" wherein $R_4"'$ is $R_4""$, R_2 is hydrogen, and m is m",

(xiv) of (xiii) wherein R_{11} is a cation in particular sodium, potassium or ammonium, especially sodium,

(xv) of Group IBb wherein Ro is Ro', R and R_1 taken together are $-(CH_2)_m-$ R_2 is R_2', R_3 is R_3', R_{10} is R_{10}', and X is X',

(xvi) of (xv) wherein Ro is Ro", R_{10} is hydrogen, and X is (E)-CH=CH-,

(xvii) of (xvi) wherein Ro is Ro"', R_2 is $R_2"$, R_3 is hydrogen, and m is m',

(xviii) of (xvii) wherein Ro is Ro"" wherein $R_4"'$ is $R_4""$, R_2 is hydrogen and m is m",

(xix)-(xxviii) of (i)-(v) and (x)-(xiv) wherein the hydroxy groups in the 3- and 5-positions of the group of formula IIa have the <u>erythro</u> configuration,

(xxix)-(xxxvi) of (vi)-(ix) and (xv)-(xviii) wherein R_{10} and the hydrogen atom in the 6-position of the group of formula IIb are <u>trans</u> to each other, i.e. the <u>trans</u> lactones,

(xxxvii) of Group IAc wherein Ro is Ro', R is R', R_1 is R_1', R_2 is R_2', R_3 is R_3' each R_7 is C_{1-3}alkyl or the two R_7's taken together are $(CH_2)_2$ or $(CH_2)_3$, R_{10} is R_{10}', R_{11} is R_{11}' and X is X' with the proviso that X may be $-CH_2CH_2-$ only when R_{10} is methyl,

(xxxviii) of (xxxvii) wherein Ro is Ro" each R_7 is C_{1-2}alkyl or the two R_7's taken together are $(CH_2)_2$ or $(CH_2)_3$, R_{10} is hydrogen, R_{11} is $R_{11}"$ and X is (E)-CH=CH-,

(xxxix) of (xxxviii) wherein Ro is Ro", R is R", R_1 is $R_1"$, R_2 is $R_2"$, R_3 is hydrogen, each R_7 is C_{1-2}alkyl and R_{11} is hydrogen or C_{1-2}alkyl, most preferably a cation,

(xl) of (xxxix) wherein Ro is Ro"" wherein R_4"' is R_4"", R is C_{1-2}alkyl, R_1 is C_{1-2}alkyl, and R_2 is hydrogen,

(xli) of (xl) wherein R_{11} is a cation, especially sodium, potassium or ammonium, particularly sodium,

(xlii) of Group IBc wherein Ro is Ro', R and R_1 taken together are $-(CH_2)_m-$, R_2 is R_2', R_3 is R_3', each R_7 is C_{1-3}alkyl or the two R_7's taken together are $-(CH_2)_{2 \text{ or } 3}-$, R_{10} is R_{10}', R_{11} is R_{11}', and X is X', with the provisos that R_{11} may be hydrogen only when Q is -CO-, and X may be $-CH_2CH_2-$ only when R_{10} is methyl,

(xliii) of (xlii) wherein Ro is Ro", each R_7 is C_{1-2}alkyl or both R_7's taken together are $-(CH_2)_{2 \text{ or } 3}-$, R_{10} is hydrogen, R_{11} is R_{11}", and X is (E)-CH=CH-

(xliv) of (xliii) wherein Ro is Ro"', R_2 is R_2", R_3 is hydrogen, each R_7 is C_{1-2}alkyl, R_{11} is R_{11}"' (especially a cation), and m is m',

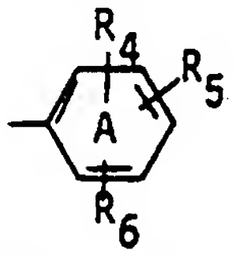
(xlv) of (xliv) wherein Ro is Ro"" wherein R_4"' is R_4"", R_2 is hydrogen, and m is m",

(xlvi) of (xlv) wherein R_{11} is a cation, particularly sodium, potassium or ammonium especially sodium and

(xlvii)-(lvi) of (xxxvii)-(xlvi) wherein Q is -CO-.

Groups (i)-(xviii) and (xxxvii)-(lvi) embrace each of the possible stereoisomers, racemates and mixtures of diastereoisomers. Groups (xix)-(xxviii) embrace the 3R,5S and 3S,5R isomers and the 3R,5S-3S,5R racemate of the compounds wherein X is (E)-CH=CH- having just two centres of asymmetry and the corresponding compounds having more than two centres of asymmetry, and Groups (xix) and(xxiv) also embrace the 3R,5R and 3S,5S isomers and the 3R,5R-3S,5S racemate of the compounds wherein X is $-CH_2CH_2-$ having just two centres of asymmetry and the corresponding compounds having more than two centres of asymmetry. Groups (xxix)-(xxxvi) embrace the 4R,6S and 4S,6R isomers and the 4R,6S-4S,6R racemate of the compounds wherein X is (E)-CH=CH- having just two centres of asymmetry and the corresponding compounds having more than two centres of asymmetry and Groups (xxix) and (xxxiii) also embrace the 4R,6R and 4S,6S isomers and the 4R,6R-4S,6S racemate of the compounds wherein X is $-CH_2CH_2-$ having just two centres of asymmetry and the corresponding compounds having more than two centres of asymmetry.

A particular compound group covers those compounds of formula I wherein

Ro represents ring A 

R is hydrogen or primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, and

R_1 is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom or

R and R_1 taken together are $-(CH_2)_m-$ or (Z)-CH_2-CH=CH-CH_2-,
wherein m is 2, 3, 4, 5 or 6,

R_2 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,
with the proviso that not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

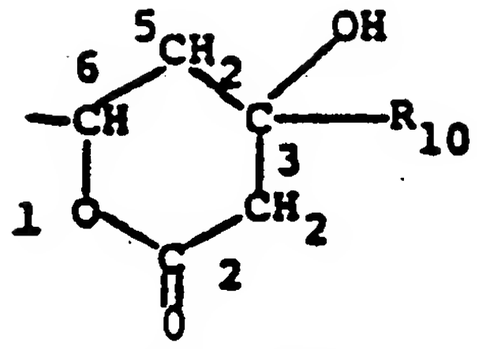
R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,
with the provisos that not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy, and not more than one of R_4 and R_5 is benzyloxy,

X is $-(CH_2)_n-$ or (E)-CH=CH-,
wherein n is 1, 2 or 3, and

Z is $-CH(OH)-CH_2-C(R_{10})(OH)-CH_2-COOR_{11}$ (a) or



(b),

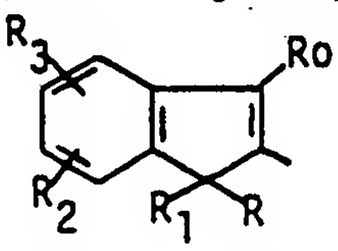
wherein R_{10} is hydrogen or C_{1-3}alkyl, and

R_{11} is hydrogen, R_{12} or M,

wherein R_{12} is a physiologically acceptable and hydrolyzable ester group, and

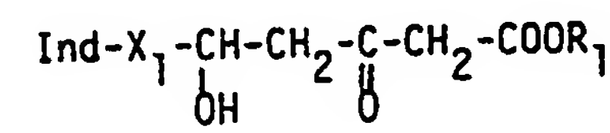
M is a pharmaceutically acceptable cation.

The compounds of formula I may be prepared by the following reactions wherein Ind stands for



and substituents are as defined above.

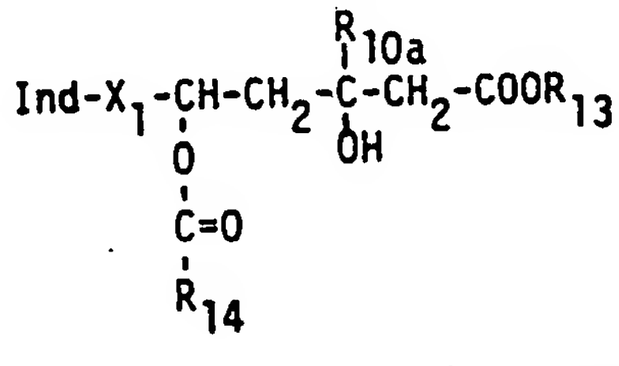
a) when X is $(CH_2)_n$ or (E)-CH=CH- and R_{10} is hydrogen reducing a compound of formula IV



IV

wherein R_{13} is a radical forming an ester, and X_1 is $(CH_2)_n$ or (E)-CH=CH-,

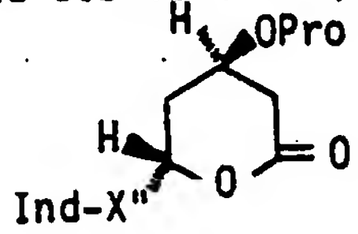
b) when X is $(CH_2)_n$ or (E)-CH=CH- and R_{10} is C_{1-3}alkyl hydrolysing a compound of formula XII



XII

wherein R_{10a} is C_{1-3}alkyl, R_{14} is part of an ester forming group and X_1 and R_{13} are as defined above,

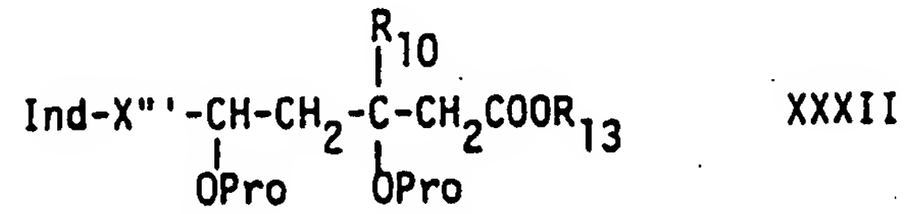
c) when X is -CH=CH- or $-CH_2$-CH=CH- and IIb is in 4R,6S configuration or X is $-CH_2CH_2$ or $CH_2CH_2CH_2$ and IIb is in 4R,6R configuration deprotecting a compound of formula XXXIX



XXXIX

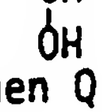
wherein X" represents $-CH_2CH_2$, $-CH_2CH_2CH_2$, -CH=CH- or $-CH_2CH=CH-$ and Pro is a protecting group,

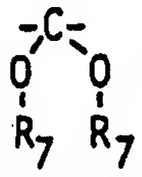
d) when X is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_qCH=CH(CH_2)_q-$ deprotecting a compound of formula XXXII



XXXII

wherein X"' is $-(CH_2)_2-$, $-(CH_2)_3-$ or $-(CH_2)_q-CH=CH-(CH_2)_q-$, and q, R_{10}, R_{13} and Pro are as defined above,

e) when Q is  oxidising the corresponding compound of formula I wherein Q is 

f) when Q is  and II is in ester form ketalising the corresponding compound of formula I wherein Q is

g) hydrolysing a compound of formula I in the form of an ester or a lactone or

h) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free acid form or in the form of a salt.

R_{13} is preferably C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl, more preferably C_{1-3}alkyl and especially C_{1-2}alkyl and R_{14} is preferably C_{1-3}alkyl more preferably n-C_{1-3}alkyl, especially C_{1-2}alkyl.

Process a) is particularly suited for compounds wherein X is $-(CH_2)_n-$ or (E)-CH=CH and in ester form.

Process b) is particularly suited for compounds wherein X is $-(CH_2)_n-$ or (E)-CH=CH in salt form.

Process c) is particularly suited for compounds wherein X is -(E)-CH=CH- and the lactone is in 4R,6S configuration and those wherein X is $-CH_2CH_2-$ and the lactone is in 4R,6R configuration.

Process d) is particularly suited for compounds in ester form.

It will readily be appreciated that the various forms of the compounds of formula I may be interconverted as indicated in g) and h) above, whereby lactonisation may only take place when Q is  and ketals cannot be isolated in free acid form or esterified.

In the same way compounds obtained according to a) to f) may be as appropriate hydrolysed to free acid forms and free acid forms may be esterified or lactonised to produce a desired end-product. The invention thus also provides a process for preparing a compound of formula I which comprises hydrolysing a compound of formula I in ester or lactone form or esterifying or lactonising a compound of formula I in free acid form and when a free carboxyl group is present recovering the compound obtained in free acid form or in the form of a salt.

Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Molar ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactions and conditions employed.

Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are usually nitrogen or a nobel gas, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned, are carried out under such for convenience.

EP 114027 and 117228 including the examples thereof disclose analogous processes and further suitable reaction conditions.

Reduction according to a) is preferably carried out using a mild reducing agent such as sodium borohydride or, a complex of t-butylamine and borane in an inert organic solvent such as a lower alkanol, preferably ethanol, conveniently at a temperature of -10° to 30°C, under an inert atmosphere.

Use of an optically pure starting material will lead to only two optical isomers (diastereoisomers) of the resulting end product. However, if stereospecificity is desired it is preferred to utilize a stereo-selective reduction in order to maximize production of a mixture of the erythro stereoisomers (racemate) of which the preferred stereoisomer (as set forth above) is a constituent. Stereoselective reduction is preferably carried out in three steps. For example in the first step, the ketoester of formula IV is treated with a tri(primary or secondary C_{2-4}alkyl)borane, preferably triethylborane or tri-n-butylborane, and optionally air to form a complex. The reaction temperature is suitably 0° to 50°C, preferably 0° to 25°C. The first step is carried out in an anhydrous inert organic solvent, preferably an ether

solvent such as tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane or 1,2-diethoxyethane, with tetrahydrofuran, being the most preferred solvent especially in a 3-4:1 mixture with methanol when pure erythro product is desired. In the second step, the complex is reduced with sodium borohydride, preferably in the same solvent as utilized for the first step, at -100° to -40°C, preferably -100° to -70°C. In the third step, the product of the second step is, for example, treated with, preferably, anhydrous methanol at 20° to 40°C, preferably 20° to 25°C. The amount of methanol is not critical. However, a large excess, e.g. 50-500 moles per mole of ketoester of formula IV is typically utilized. Alternatively a mixture of methanol, e.g. 30% aqueous H_2O_2 and a pH 7-7.2 aq. phosphate buffer is used.

Hydrolysis according to b) or g) is carried out in a manner conventional for such reactions e.g. employing an inorganic hydroxide such as NaOH or KOH with, if desired subsequent acidification to give the free acid form. Suitable solvents are mixtures of water and water miscible solvents such as lower alkanols e.g. methanol or ethanol and reaction conveniently takes place at temperatures from 0°C to reflux preferably 0° to 75°C e.g. 20° to 70°C. If it is desired to recover the compound in a salt form corresponding to the cation of the hydroxide employed then slightly less than equivalent amounts of the latter may be employed. In b) R_{14} will conveniently be the same as R_{13} e.g. C_{1-3}alkyl more preferably n-C_{1-3}alkyl, especially C_{1-2}.

Oxidation according to e) can be carried out when X is -CH=CH- or $-CH_2CH=CH-$ using activated MnO_2 at 20° to 80°C, preferably 40° to 80°C in an anhydrous inert organic solvent such as an ether solvent e.g. $(C_2H_5)_2O$, 1,2-diethoxyethane, 1,2-dimethoxyethane, tetrahydrofuran and mixtures thereof, or when X is $(CH_2)_n$ or $-CH=CH-CH_2$ using Swerns reagent (oxalyl chloride + dimethylsulfoxide) with triethylamine in e.g. $-CH_2Cl_2$ at -60° to -40°C preferably -50°C.

Ketalisation according to f) can be carried out in the case of open chain ketals using $H-C(OR_7)_3$ in the presence of catalytic amounts of pyridinium p-toluene sulfonate and a hydrocarbon solvent, for example benzene, toluene, xylene and mixtures thereof, halogenated lower alkane solvent, for example carbon tetrachloride, chloroform, 1,1-dichloroethane, 1,2-dichloroethane, methylene chloride and 1,1,2-trichloroethane, usually preferably methylene chloride or benzene at 20-25°C or for cyclic ketals using $HO-(CH_2)_{2-3}-OH$ under the same conditions.

Lactonisation according to h) is carried out in conventional manner e.g. by heating the corresponding acid in anhydrous inert organic solvent e.g. a hydrocarbon such as benzene, toluene or a xylene or mixtures thereof, preferably at temperatures of 75°C to reflux although more preferably not above 150°C. Preferably, however, a lactonisation agent, e.g. a carbodiimide, preferably a water-soluble carbodiimide such as N-cyclohexyl-N'-[2'-(methylmorpholinium)ethyl]carbodiimide p-toluenesulfonate, in an anhydrous inert organic solvent, e.g. a halogenated lower alkane, preferably methylene chloride is employed. Reaction temperatures then lie typically between 10° and 35°C, especially 20° to 25°.

As is evident to those in the art, a racemic threo 3,5-di-hydroxy-carboxylic acid yields a racemic cis lactone (two stereoisomers) and a racemic erythro 3,5-dihydroxycarboxylic acid yields a racemic trans lactone (two stereoisomers). Likewise if a single enantiomer of the 3,5-dihydroxycarboxylic acid is utilized, a single enantiomer of the lactone is obtained. For example, lactonisation of a 3R,5S erythro dihydroxycarboxylic acid yields a 4R,6S lactone.

Esterification according to h) is conventional, employing e.g. a large excess of a compound $R_{13}OH$, wherein R_{13} is as defined above at e.g. 20°C to 40°C in the presence of a catalytic amount of an acid such as p-toluenesulfonic acid. Direct esterification is particularly suited when Q is -C-.
‖
O

Preferably, however, esterification takes place by first forming the corresponding lactone and reacting this with $M_2^{\oplus}\ ^{\ominus}OR_{13}$ ($M_2^{\oplus}$=$Na^{\oplus}$ or $K^{\oplus}$) at 0° to 70°C preferably 20° to 25°C in an inert organic solvent e.g. an ether such as tetrahydrofuran or an alcohol of formula $R_{13}OH$ if a liquid.

Examples of protecting groups in reaction c) and d) are diphenyl-t-butylsilyl, tri-isopropylsilyl or dimethyl-t-butylsilyl, benzyl, triphenylmethyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, 4-methoxytetrahydrofuran-4-yl, C_{2-6}n-alkanoyl. Especially preferred

are trisubstituted silyl radicals in particular diphenyl-t-butylsilyl (=Pro').

Deprotection is carried out in conventional manner e.g. by cleavage under mild conditions such as employing e.g. for removal of a diphenyl-t-butylsilyl a fluoride reagent e.g. tetra-n-butylammonium fluoride in an anhydrous inert organic medium preferably tetrahydrofuran containing glacial acetic acid at temperatures of 20° to 60°C, especially 20° to 25°C. Preferably 1-4 moles of fluoride per mole protecting group are used with 1-2 moles, preferably 1.2 to 1.5 mmoles of glacial acetic acid to each mole of fluoride.

The required starting materials may be prepared for example as illustrated in the following reaction schemes or in the examples hereinafter.

Further suitable reaction conditions are disclosed e.g. in EP 114027 and 117228 including the examples thereof.

Abreviations:

AIO - anhydrous inert organic solvent

ES - ether solvent e.g. diethylether, 1,2-diethoxyethane, 1,2-dimethoxyethane, THF or mixtures thereof

HC - hydrocarbon solvent e.g. benzene, toluene, xylene or mixtures thereof

HLA - halogenated lower alkane solvent e.g. CCl_4, $CHCl_3$, 1,1-dichloroethane, 1,2-dichloroethane, methylene chloride, 1,1,2,-trichloroethane, preferably CH_2Cl_2

IO - inert organic solvent

THF - tetrahydrofuran

LDA - lithiumdiisopropylamide

nBuLi - n-butyllithium

DMF - dimethylformamide

DIBAH - diisobutylaluminium hydride

Variables not previously defined

R_{15} is C_{1-2}alkyl, preferably methyl

X_2 is CH_2 or $(CH_2)_2$

X_3 is a direct bond or CH_2

X_4 is -CH=CH-, -CH=CH-CH_2- or -CH_2-CH=CH- preferably (E)-CH=CH-, (E)-CH=CH-CH_2- or (E)-CH_2-CH=CH- especially (E)-CH=CH-,

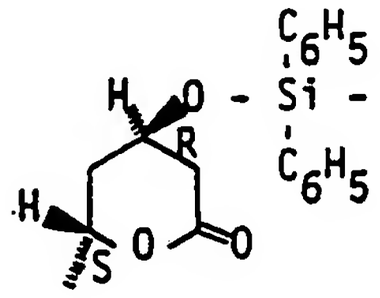
X_5 is $(CH_2)_2$- or -$(CH_2)_3$- especially -$(CH_2)_2$-

X_6 is -CH=CH- or -CH_2-CH=CH-, preferably CH=CH and especially (E)-CH=CH-

Y is Cl, Br or I

Y' is Cl or Br

Lac_1 =



C_6H_5
Si - t - C_4H_9
C_6H_5

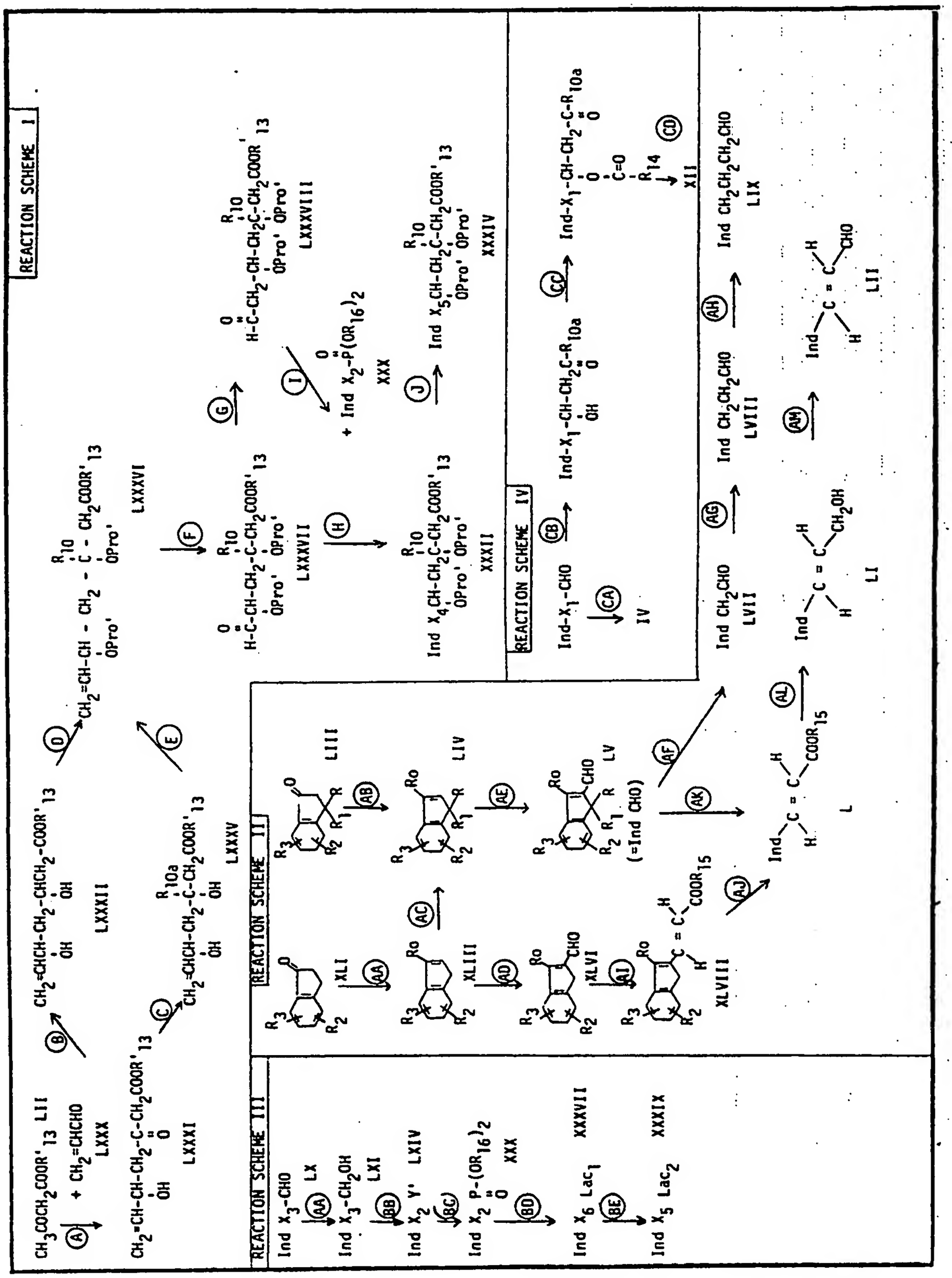
Lac_2 = as Lac_1 but in 4R,6R configuration

C_6H_5
Pro' = - Si - t - C_4H_9
C_6H_5

R_{13}' is C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl

each R_{16} is independently CH_3 or C_2H_5 and they are preferably the same

R_{17} is R_1, $(CH_2)_m$-Y' or (Z)-CH_2-CH=CH-CH_2-Y'


REACTION SCHEME I
REACTION SCHEME II
REACTION SCHEME III
REACTION SCHEME IV
CH3COCH2COOR'13 LII
CH2=CHCH-CH2-CHCH2-COOR'13
OH OH
LXXII
CH2=CHCH-CH2-C-CH2COOR'13
OH O
LXXXI
CH2=CHCH-CH2-C-CH2-COOR'13
OH
LXXV
CH2=CH-CH-CH2-C-CH2COOR'13
OPro' OPro'
LXXVI
H-C-CH2-CH-CH2-C-CH2COOR'13
O OPro' OPro'
LXXVII
Ind X4CH-CH2-C-CH2COOR'13
OPro' OPro'
XXXII
H-C-CH2-CH-CH2-C-CH2-COOR'13
O OPro' OPro'
LXXVIII
Ind X5CH-CH2-C-CH2COOR'13
OPro' OPro'
XXXIV
Ind-X1-CHO
Ind-X1-CH-CH2-C-R10a
OH O
Ind-X1-CH-CH2-C-R10a
O O
C=O
R14
XII
Ind CH2CH2CHO
LIX
Ind CH2CH2CHO
LVIII
Ind CH2CH2CHO
LVII
+ Ind X2-P(OR16)2
O
XXX
Ro
CHO
R3
R2 R1
(=Ind CHO)
LV
Ind
C = C
H
CHO
LII
CH2OH
LI
COOR15
L
LIII
LIV
XLI
XLIII
XLVI
XLVIII
A
B
C
D
E
F
G
H
I
J
CA
CB
CC
CD
AA
AB
AC
AD
AE
AF
AG
AH
AI
AJ
AK
AL
AM
AN
BA
BB
BC
BD
BE
REACTION SCHEME III
Ind X3-CHO
Ind X3-CH2OH
Ind X2 Y' LXIV
Ind X2 P-(OR16)2
O
XXX
Ind X6 Lac1
XXXVII
Ind X5 Lac2
XXXIX
LX
LXI

REACTION	TYPE / STEPS	SPECIAL CONDITIONS/REACTIONS	TEMPERATURE	ATMOS.	SOLVENT
(A)		1. Strong base e.g.LDA or NaH followed by n-BuLi to generate dianion	① -50° to 10° pref. -10° to 10°	Inert	AIO e.g. ES pref. THF
		2. Add LII	② -80° to 0°, pref. -40° to -20° esp. -35° to -30° rising to 20°-25°		
		3. Quench with e.g. NH_4Cl	③ -80° to 25°		
(B)	Reduction	As process a) above	→	→	→
(C)	Grignard	$R_{10a}MgY$ (LXXXIV) quench on completion e.g. with NH_4Cl	-70° to 25° pref. -50° to 0°	Inert	as A
(D)(E)	Silylation	2-8 moles pref. 4 moles of Pro'Cl per mole LXXXII or LXXXV + 2 moles of imidazole per mole Pro'Cl	20° to 30° pref. 20 to 25°	Inert	anh. DMF
(F)	Ozonolysis	O_3 in excess; then quench with $(CH_3)_2S$ or $(C_6H_5)_3P$	-80° to -70° pref. -78°	-	C_{1-3}alkanol esp. CH_3OH or HLA esp. CH_2Cl_2 or $CH_3COOC_2H_5$
(G)	Wittig	① $(C_6H_5)_3\overset{\oplus}{P}-CH_2OCH_3Cl^{\ominus}$ (LVI) + strong base e.g. NaH, phenyl lithium or nBu-Li	1. -40 to 0° pref. -35° to -20°	Inert	as A
		② Add LXXXVII	2. -30° to 0° pref. -20° to 0°	"	"
		③ hydrolysis: excess of strong acid e.g. aq. perchloric	3. 0° to 30°	-	e.g. acid + ES e.g. aq. perchloric + THF

REACTION	TYPE / STEPS	SPECIAL CONDITIONS/REACTIONS	TEMPERATURE	ATMOS.	SOLVENT
(H), (I)		① strong base e.g. nBuLi or LDA	1) -10° to 0°	Inert	as (A)
		② add LXXXVII or LXXXVIII	2) -10° to 0°	"	as (A)
(J)	Hydrogenation	H_2 at raised pressure (e.g. 30-60 psi) PtO_2 as catalyst	20° to 25°	-	Loweralkanol e.g. C_2H_5OH
(AA), (AB)	Grignard + dehydration	① Ro-MgY (XL II) + opt. trace of CH_3I or 1,2-dibromo-ethane	10° to reflux pref. 30° to 38° in $(C_2H_5)_2O$ and 35° to 65° in THF	Inert	AIO e.g. ES esp. THF or $(C_2H_5)_2O$
		② add XLI or LIII	20° to 25°	"	" "
		③ e.g. with glacial CH_3COOH or HCl	90° to, esp. 100° to, pref. 100° to reflux	-	Neat
(AC), (AJ)	Alkylation	① generation of mono- or di-carbanion with NaH	0° to 25° esp.10-25° -5° to 5° pref. 0°	Inert	AIO pref. ES e.g. THF or HC e.g. toluene pref. toluene
		② when R is H and R_1 is alkyl or together they are $(CH_2)_m$- or (Z)-CH_2-CH=CH-CH_2 1-1.05 moles of $R_{17}Y'$; when R and R_1 identical alkyl 2-2.1 moles. For different alkyls as R, R_1 repeat reaction	0° to 25°	"	" "

REACTION	TYPE / STEPS	SPECIAL CONDITIONS/REACTIONS	TEMPERATURE	ATMOS.	SOLVENT
(AD), (AE)	Vilsmeier-Haack	① C_6H_5-NCHO + $POCl_3$ CH_3	0° to 35°, pref. 20° 25°	Inert	Acetonitrile or neat
		② add XLIII or LIV	10° to 30° pref. 10° rising to 20° to 25°	"	" "
		③ hydrolysis (H_2O)	0° to 25°	-	water
(AF), (AG) (AH)	Wittig	as (G)	→	→	→
(AI), (AK)	Wittig	$(C_6H_5)_3P$ = CH-$COOR_{15}$	50° to reflux pref. 60° to 115° esp. 90° to 115°	"	as (AC)
(AL)	Reduction	Strong metal hydride e.g. $LiAlH_4$ or DIBAH	-80° to 25° pref. -80° to 0° esp. -80° to -70°	"	AIO pref. ES e.g. THF; HLA esp. CH_2Cl_2 or HLA + toluene
(AM)	Oxidation	excess activated MnO_2	20° to 30° pref. 20° to 25°		IO pref. HLA esp. CH_2Cl_2 or HC esp. toluene
(BA)	Reduction	non-stereospecific as is a)	→	→	→
(BB)	Halogenation	SOY'_2 or PY'_3	-10° to 80°	-	AIO pref. ES eq. $(C_2H_5)_2O$ or THF; HLA e.g. CH_2Cl_2; or HC e.g. benzene
(BC)		add $P(OR_{16})_3$	20° to 140° usually 110° to 140°	yes	HC e.g. benzene or xylene or neat with excess $P(OR_{16})_3$
(BD)	Wittig	as (H)	→	→	→
(BE)	Hydrogenation	as (J)	→	→	→

The conditions given hereinabove are largely conventional for such reactions and can be varied in conventional manner according to the particular intermediates/end products. This applies e.g. to molar ratios, temperature, reaction times and the like which are chosen according to principles well established in the art on the basis of reactants and conditions employed.

Intermediates, the production of which is not described above, are either known or may be prepared according to or analogously to known methods e.g. as described in EP 114027 and 117228 including the examples thereof. Process CA to CD are for example described in EP 114027.

Reaction products, both intermediates and final, can be isolated (e.g. from compound mixtures or reaction mixtures) and purified in conventional manner whereby intermediates can, where appropriate, be employed directly in a subsequent reaction.

Mixtures of stereoisomers (cis, trans and optical) can be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystallisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthylphenylmethylsilyl derivatives of a lactone type end product of formula I may be separated by conventional means.

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. In some cases e.g. for groups IAc, IBc in ketal form ion-exchange may be required for salt formation. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae IV, XII, XXXII, XXXIV, XXXVII, XXXIX, XLVI, XLVIII, L-LII, LV, LVII-LIX, LX, LXI, LXIV and products of reactions CB and CC.

The preferences for each variable are the same as set out for formula I and preferred groups of compounds correspond to those listed for formula I as appropriate to and consistent therewith.

The compounds of formula I possess pharmacological activity in particular as competitive inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence are inhibitors of cholesterol biosynthesis as demonstrated in the following tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:
As described in EP 114027 or 117228 (dosage range 0.0001-2000 µmol).

Test B: In Vivo Cholesterol Biosynthesis Inhibition
As described in EP 114027 or 117228 (dosage range 0.01-200 mg/kg).

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of hyperlipoproteinemia and atherosclerosis is from about 1 to 2000 mg preferably 1 to 150 mg suitably administered one to four times daily or in controlled release form. A typical dosage unit for oral administration may contain 0.25 to 500 mg.

The compounds of formula I may be administered in similar manner as known compounds suggested for use in such indications e.g. Compactin or Mevinolin. The suitable daily dosage for a particular compound will depend a number of factors such as its relative potency of activity. It has, for example been determined that the preferred compound (compound of example no. 2) obtained an ED_{50} of 0.07 mg/kg in Test B compared with 3.5 mg/kg for Compactin and 0.41 mg/kg for Mevinolin. It is therefore indicated that the compounds may be administered at similar or significantly lower dosages (e.g. 1 - 30 mg/d) than conventionally proposed e.g. for Compactin.

The invention therefore also concerns a method of treating hyperlipoproteinemia or atherosclerosis by administration of a compound of

formula I in free acid form or in the form of a physiologically-acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form as well as such compounds for use as pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

EXAMPLE 1

Ethyl erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-spiro[cyclopentane-1,1'-(1H)-inden]-2'-yl]hept-6-enoate (Cmpd. No. 1)

Step 1 (Reaction AA)

3-(4'-Fluorophenyl)-1H-indene (Compound XLIIIa)

A solution of 5.1 g (39 mmoles) of 1-indanone in 15 ml of anhydrous diethyl ether is added over a 30 minute period to a solution of 4-fluorophenylmagnesium bromide (prepared from 7.97 g (45.5 mmoles) of 1-bromo-4-fluorobenzene, 1.33 g (54.7 mmoles) of magnesium turnings and a trace of iodine in 25 ml of anhydrous diethyl ether) stirred at 20°-25°C under nitrogen. The reaction mixture is stirred at 20°-25°C under nitrogen for 16 hours and quenched with saturated ammonium chloride solution. The organic phase is separated, dried over anhydrous sodium sulfate and evaporated at reduced pressure, and the residual oil is dissolved in 16 ml of glacial acetic acid.

The obtained solution is refluxed for 15 minutes, and the acetic acid is evaporated at reduced pressure. The residue is flash chromatographed on a silica gel column utilizing 10% ethyl acetate/petroleum ether as the eluant, and the eluant is evaporated at reduced pressure to obtain a solid which is recrystallized from 95% ethanol to obtain the product, m.p. 38-40°C.

Step 2 (Reaction AD)

3-(4'-Fluorophenyl)-1H-indene-2-carboxaldehyde (Cmpd. XLVIa)

5 ml of acetonitrile is added to a mixture of 0.973 ml (10 mmoles) of phosphorus oxychloride and 1.3 ml (10 mmoles) of N-methylformanilide stirred at 20°-25°C, the reaction mixture is stirred at 20°-25°C for 30 minutes and cooled to 5°C, a solution of 2 g (9.5 mmoles) of XLIIIa in 5 ml of acetonitrile is added dropwise with stirring, and the reaction mixture is stirred at 20°-25°C for 6.5 hours, the reaction mixture being maintained under nitrogen throughout. The reaction mixture is poured onto ice and extracted several times with 4:1 diethyl ether/petroleum ether. The extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, passed through a short silica gel column and evaporated at

reduced pressure to obtain the crude product as an oil. The oil is dissolved in chloroform and flash chromatographed on a silica gel column, the eluant is evaporated at reduced pressure, and the residue is crystallized from petroleum ether to obtain the product, m.p. 70°-71°C.

Step 3 (Reaction AI)

Methyl (E)-3-[3'-(4"-fluorophenyl)-1H-inden-2'-yl]propenoate Compound XLVIIIa)

A solution of 573 mg (2.42 mmoles) of Compound XLVIa and 1.01 g (2.91 mmoles) of (carbomethoxymethylene)triphenylphosphorane in 6 ml of dry toluene is refluxed under nitrogen for 7 hours. The reaction mixture is cooled to 20°-25°C, diethyl ether is added, and the mixture is filtered through a short silica gel column. The eluate is evaporated at reduced pressure to obtain a yellow oil which is crystallized from 95% ethanol to obtain the product, m.p. 121°-122°C.

Step 4 (Reaction AJ)

Methyl (E)-3-[3'-(4"-fluorophenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]propenoate (Compound La)

112 mg (2.3 mmoles) of sodium hydride (as a 50% by weight dispersion in mineral oil) is added to a solution of 340 mg (1.16 mmoles) of compound XLVIIIa in 5 ml of dry dimethylformamide stirred at 0°C, the reaction mixture is stirred at 0°C for 10 minutes, 0.143 ml (1.16 mmoles) of 1,4-dibromobutane is added dropwise with stirring over a 5 minute period, and the reaction mixture is allowed to gradually warm to 20°-25°C with stirring and stirred at 20°-25°C for 16 hours, the reaction mixture being maintained under nitrogen throughout. The reaction mixture is diluted with diethyl ether, dilute hydrochloric acid is added, and the mixture is extracted three times with diethyl ether. The diethyl ether extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to dryness at reduced pressure. The residue is chromatographed on a silica gel column utilizing 4:1 petroleum ether/acetone as the eluant to obtain the product, m.p. 143°-145°C.

Step 5 (Reaction AL)

(E)-3-[3'-(4"-fluorophenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-prop-2-en-1-ol (Compound LIa)

2 ml of 1.5M diisobutylaluminium hydride/toluene (3 mmoles) is added dropwise to a solution of 220 mg (0.632 mmole) of Compound La in 4 ml of dry methylene chloride stirred at -78°C under nitrogen, and the reaction mixture is stirred under the same conditions for 20 minutes, quenched with dilute hydrochloric acid and extracted several times with methylene chloride. The methylene chloride extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated at reduced pressure to obtain the product which solidifies upon standing, m.p. 102°-104°C.

Step 6 (Reaction AM)

(E)-3-[3'-(4"-fluorophenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-prop-2-enal (Compound LIIa)

300 mg (3.45 mmoles) of activated manganese dioxide is added to a solution of 170 mg (0.531 mmole)) of Compound LIa in 4 ml of dry toluene stirred at 20°-25°C, and the reaction mixture is stirred at 20°-25°C under nitrogen for 24 hours, filtered to remove the manganese dioxide and evaporated at reduced pressure to obtain the yellow product which solidifies upon standing, m.p. 123-125°, following recrystallisation from diethylether/petroleum ether, 129°-130°C.

Step 7 (Reaction CA)

Ethyl (E)-7-[3'-(4"-fluorophenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-5-hydroxy-3-oxohept-6-enoate (Compound IVa)

(a) A stock solution of the dianion of ethyl acetoacetate is prepared as follows: 7.5 ml of 1.6M n-butyllithium/hexane (12.0 mmoles) is added over a period of 5 minutes to a solution of 1.23 g (12.2 mmoles) of diisopropylamine in 25 ml of dry tetrahydrofuran stirred at -5°-0°C under nitrogen, the rate of addition being such that the temperature does not exceed 5°C. The reaction mixture is stirred at -30°C for 15 minutes under nitrogen, 780.8 mg (6 mmoles) of ethyl acetoacetate (dried over molecular sieves) is slowly added, and the reaction mixture is stirred at -30° to -20°C under nitrogen for 45 minutes.

(b) 3.3 ml of the stock solution of the dianion of ethyl acetoacetate of Part (a) (0.6 mmoles) is added to a solution of 126 mg (0.396 mmole) of Compound LIIa in 3 ml of dry tetrahydrofuran stirred at -60°C under nitrogen, and the reaction mixture is stirred under the same conditions for 1 hour, quenched with water, acidified with dilute hydrochloric acid and extracted three times with ethyl acetate. The ethyl acetate extracts are combined, washed with water, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to dryness at reduced pressure. The residue is purified by preparative thin layer chromatography on silica gel plates utilizing 4:1 petroleum ether/acetone as the solvent to obtain the product as a pale yellow oil.

The product is a racemate that may be resolved by conventional means to obtain the 5R and 5S enantiomers.

Step 8 (Reaction a))

Ethyl erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]hept-5-enoate (Compound No. 1)

(a) 0.8 ml of 1M. triethylborane/tetrahydrofuran (0.8 mmole) is added to a solution of 300 mg (0.67 mmole) of Compound IVa in 10 ml of dry tetrahydrofuran stirred at 20°-25°C, 0.2 ml of air is added via syringe, the reaction mixture is stirred at 20°-25°C for 2 hours and cooled to -78°C, 0.06 g (1.59 mmoles) of sodium borohydride is added in one portion, and the reaction mixture is stirred at -78°C for 48 hours, the reaction mixture being maintained under nitrogen throughout. The cooling bath is removed, and 1N. hydrochloric acid is slowly added dropwise until the evolution of hydrogen ceases and the mixture is acidic (pH$\sim$5), the internal temperature of the mixture being maintained below -20°C throughout. 10 ml of water is added, the mixture is extracted three times with diethyl ether, and the diethyl ether extracts are combined, washed twice with water, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated at reduced pressure to obtain a crude oil.

(b) A solution of the product of Part (a) in 5 ml of methanol is stirred at 20°-25°C for 66 hours under nirogen and evaporated to dryness at reduced pressure. The residue is chromatographed on a silica gel column utilizing 1:1 diethyl ether/petroleum ether as the eluant to obtain the crude product which solidifies on standing. Repeated recrystallisation from diethyl ether/hexane give the product as a white solid, m.p. 90°-93°C.

N.M.R. ($CDCl_3$) : 1.3 (t, 3H), 1.6-1.9 (m, 4H), 2.2 (m, 6H), 2.5 (m, 2H), 3.2 (bs, 1H), 3.7 (bs, 1H), 4.15 (q, 2H), 4.25 (m, 1H), 4.45 (m, 1H), 5.8 (dd (J_1=8 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz.), 1H), 7.0-7.5 (m, 8H)

EXAMPLE 2

Sodium erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]hept-6-enoate (Compound no. 2)

0.11 ml of 1N. sodium hydroxide solution (0.11 mmole) is added to a solution of 50 mg (0.111 mmole) of Compound No. 1 in 3 ml of absolute ethanol stirred at 0°C, and the reaction mixture is stirred at 0°C under nitrogen for 1.5 hours and evaporated to dryness at reduced pressure. The residue is washed three times with diethyl ether to obtain the product, m.p. > 170°C (dec.).

N.M.R. ($CDCl_3$+CD_3OD) : 1.5-2.5 (m, 12H), 4.1 (m, 1H), 4.3 (m, 1H), 5.8 (dd (J_1=8 Hz., J_2=20 Hz.), 1H), 6.4 (d (J=20 Hz.), 1H), 7.0-7.5 (m, 8H)

Compounds 1 and 2 are about 24:1 mixtures of the erythro and threo racemates which may be separated by conventional means. The principal product, the erythro racemate, may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The minor product, the threo racemate, may be resolved into the 3R,5R and 3S,5S isomers, of which the former is preferred. The use of a starting material synthesized by utilizing a non-stereoselective reduction would afford a mixture of all four stereoisomers wherein the ratio of the erythro isomers to the threo isomers ranges from 3:2 to 2:3.

EXAMPLE 3

(E)-3,5-dihydroxy-7-[3'-(3",5"-dimethylphenyl)spiro[cyclopentane-1,1'-(1H)-inden]-2'-yl]hept-6-enoic acid, its sodium salt and its ethyl ester (Compounds Nos. 3, 4 and 5)

(a) 31 ml of 1M. triethylborane/tetrahydrofuran (31 mmoles) is added to a solution of 12.0 g (≤26.2 mmoles) of ethyl (E)-7-[3'-(3",5"-dimethylphenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-5-hydroxy-3-oxo-hept-6-enoate (Compound IVb) (preparable analogously to Example 1 steps 1 to 7) in 500 ml of dry tetrahydrofuran stirred at 20°-25°C, 50 ml of air (at 25°C and 760 mm Hg.) is added via a syringe, the reaction mixture is stirred at 20°-25°C for 2 hours and cooled to -78°C, 1.14 g (30.2 mmoles) of sodium borohydride is added in one portion, and the reaction mixture is stirred for 16 hours at -78°C and allowed to warm to 20°-25°C, the reaction mixture being maintained under nitrogen throughout. The reaction mixture is evaporated to dryness at reduced pressure, the residue is vacuum dried, diethyl ether is added, the insoluble material is removed by filtration, and the filtrate is evaporated at reduced pressure. 50 ml of water is added to the oily residue, and the mixture is extracted twice with diethyl ether. The diethyl ether extracts are combined and cooled to 0°C, 10 ml of methnol, 5 ml of 30% aqueous hydrogen peroxide and 10 ml of an aqueous phosphate buffer having a pH of 7 (0.054M. sodium, 0.024M. potassium and 0.047M. phosphate) are added, and the reaction mixture is stirred at 0°C under nitrogen for 45 minutes. Most of the diethyl ether and methanol is evaporated at reduced pressure, the residual aqueous solution is extracted with diethyl ether three times, and the diethyl ether extracts are combined and evaporated at reduced pressure to obtain the crude product as a yellow oil (Compound No.5).

N.M.R. ($CDCl_3$) : 1.25 (t, 3H), 1.6-2.3 (m, 10H), 2.4 (s, 6H), 2,5 (m, 2H), 3.5 (s, 1H), 3.7 (d, 1H), 4.15 (q, 2H), 4.25 (m, 1H), 4.4 (m, 1H), 5.7 (dd, 1H), 6.5 (d (J=20 Hz.), 1H), 6.95-7.4 (m, 7H)

(b) The aqueous layer from the initial diethyl ether extraction (prior to the addition of methanol, hydrogen peroxide and buffer) is acidified with dilute hydrochloric acid, and the mixture is extracted twice with ethyl acetate. The ethyl acetate extracts are combined, dried over anhydrous sodium sulfate, filtered and evaporated at reduced pressure to obtain the crude compound as a foam (Compound No. 3).

(c) 6.5 ml of 1N. sodium hydroxide solution (6.5 mmoles) is added to a solution of 3 g (≤ 6.5 mmoles) of the crude compound (from Part (a)) in 25 ml of ethanol stirred at 0°, and the reaction mixture is stirred at 0°C under nitrogen for 30 minutes, washed with diethyl ether, acidified with dilute hydrochloric acid and extracted with diethyl ether twice. The diethyl ether extracts are combined, dried over anhydrous sodium sulfate, filtered and evaporated at reduced pressure to obtain Compound No. 3 as an oil.

The reaction mixture, prior to the acidification, contains the sodium salt of Compound No. 3 (Compound No. 4). It may be isolated and purified conventionally. m.p. > 160°C (dec.).

N.M.R. ($CDCl_3$+CD_3OD) : 1.5-2.35 (m, 12H), 2.3 (s, 6H), 4.1 (m, 1H), 4.3 (m, 1H), 5.75 (dd, 1H), 6.45 (d (H=20 Hz.), 1H), 6.95-7.4 (m, 7H)

Compounds 3, 4 and 5 are approximately 3-9:1 mixtures of the erythro and threo racemates which may be separated by conventional means, e.g. lactonization of the free acid, separation of the cis and trans lactones, hydrolysis of the lactones, etc. The principal product, the erythro racemate in each case, may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R enantiomers, of which the former is preferred. The minor product, the threo racemate in each case, may be resolved to obtain the 3R,5R and 3S,5S enantiomers, of which the former is preferred. The use of a non-stereoselective reduction would afford a mixture of all four stereoisomers wherein the ratio of the erythro stereoisomers to the threo stereoisomers ranges from 3:2 to 2:3.

EXAMPLE 4

(E)-Trans-6-(2'-[3"-(3"',5"'-dimethylphenyl)spiro[cyclopentane-1,1'-(1H)-inden]-2"-yl]ethenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (Compound No. 6) and the corresponding cis lactone (Compound No. 7)

(a) 8.7 g (20.5 mmoles) of N-cyclohexyl-N'[2'-(N"-methylmorpholinium) ethyl]carbodiimide p-toluenesulphonate is added to a solution of 8.7g (≥ 20.1 mmoles) of Compound No. 3 in 250 ml of methylene chloride (freshly filtered through basic alumina), and the reaction mixture is stirred at 20°-25°C under nitrogen for about 3 hours (until no Compound No. 3 is detectable by thin layer chromatography) and evaporated to dryness at reduced pressure. Water is added, and the mixture is extracted three times with diethyl ether. The diethyl ether extracts are combined, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to dryness at reduced pressure to obtain an about 3-4:1 mixture of Compounds No. 6 and No. 7 as a yellow foam.

(b) The product of Part (a) is separated on a Waters Prep-500 high pressure liquid chromatography apparatus utilizing a silica gel column and 15:4.5:10.5 n-hexane/acetonitrile/methyl t-butyl ether to elute the trans lactone (Compound No. 6), a solid foam.

N.M.R. ($CDCl_3$) : 1.7-2.3 (m, 10H), 2.35 (s, 6H), 2.7 (m, 2H), 4.4 (m, 1H), 5.25 (m, 1H), 5.75 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.55 (d (J=20 Hz.), 1H), 6.9-7.5 (m,7H)

Also eluted from the column is the cis lactone (Compound No. 7), also a solid foam.

N.M.R. ($CDCl_3$) : 1.7-2.5 (m, 10H), 2.35 (s, 6H), 2.8 (m, 2H), 4.3 (m, 1H), 4.7 (m, 1H), 5.75 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz) Hz.), 1H), 6.95-7.4 (m,7H)

Compounds No. 6 and No. 7 are both racemates that may be resolved by conventional means to obtain, in the case of the former, the 4R,6S and 4S,6R enantiomers, of which the former is preferred, and, in the case of the latter, the 4R,6R and 4S,6S enantiomers, of which the former is preferred.

EXAMPLE 5

Sodium erythro-(E)-3,5-dihydroxy-7-[3'-(3",5"-dimethylphenyl)-spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]hept-6-enoate (Compound No. 8) and

Sodium threo-(E)-3,5-dihydroxy-7-[3'-(3",5"-dimethylphenyl)-spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]hept-6-enoate (Compound No. 9)

0.16 of 1N. sodium hydroxide solution (0.16 mmole) is added to a solution of 70 mg (0.169 mmole) of Compound No. 6 in 3 ml of absolute ethanol stirred at 0°C, and the reaction mixture is stirred at 0°C under nitrogen for 30 minutes and evaporated to dryness at reduced pressure. The residue is washed with anhydrous diethyl ether and vacuum dried to obtain the product as a pale yellow solid m.p.> 170°C (dec.)

N.M.R. ($CDCl_e$+CD_3OD) : 1.5-2.35 (m, 12H), 2.3 (s, 6H), 4.1 (bs, 1H), 4.3 (bs, 1H), 5.75 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.45 (d (J=20 Hz.), 1H), 6.95-7.4 (m,7H)

Compound No. 9 is prepared analogously from Compound No. 7.

m.p. 160°C (dec.)

N.M.R. ($CDCl_3$+CD_3OD) : Essentially the same as that of Compound No.8

Compounds Nos. 8 and 9 are racemates that may be resolved by conventional means to obtain the 3R,5S and 3S,5R enantiomers (no. 8) and 3R,5R and 3S,5S (No. 9), of which the former in each case are preferred.

EXAMPLE 6

Ethyl (±)-(E)-7-[3'-(4"-fluorophenyl)-spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-3-hydroxy-5-oxohept-6-enoate (Compound No.10)

A mixture of 310 mg of Compound No. 1, 600 mg of activated manganese dioxide and 5 ml of toluene is stirred under nitrogen at 20°-25°C for 24 hours, at 60°C for 8 hours, at 20°-25°C for 16 hours and at 80°C for 8 hours and allowed to cool to 20°-25°C. Diethyl ether is added, the mixture is filtered and the filtrate is evaporated at reduced pressure to obtain an oil. The oil is purified by preparative thin layer chromatography on silica gel plate utilizing 80% diethyl ether/ petroleum ether as the solvent. The band containing the product is scraped and eluted with ethyl acetate and the solution is filtered

and evaporated at reduced pressure to obtain the product as a yellow solid, m.p. 107°-109°C.

The product is a racemate that may be resolved by conventional means to obtain the 3R and 3S enantiomers.

EXAMPLE 7

Ethyl (±)-(E)-5,5-dimethoxy-7-[3'-(4"-fluorophenyl)spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-3-hydroxyhept-6-enoate (Compound No.11)

A mixture of 90 mg ofCompound No. 10, 0.1 ml of trimethyl ortho-formate, 2 mg of pyridinium p-toluenesulfonate and 3 ml of methylene chloride is stirred under nitrogen for 45 hours at 20°-25°C and evaporated at reduced pressure, and the residual oil is purified by preparative thin layer chromatography on a silica gel plate utilizing 60% diethyl ether/petroleum ether as the solvent. The band containing the product is scraped and eluted with ethyl acetate and the solution is filtered and evaporated at reduced pressure to obtain the product as a yellow oil.

The product is a racemate that may be resolved by conventional means to obtain the 3R and 3S enantiomers.

The following compounds may be prepared analogously or as otherwise described hereinbefore.

TABLE I

Compounds of Group IAa (wherein Ro is ring A)

Cmpd. No.	R	R_1	R_2, R_3	R_4,R_5,R_6	X	R_{10}	R_{11}	Isomers	m.p.
12	H	$\underline{i}$-C_3H_7	H	4-F	(E)-CH=CH-	H	C_2H_5	D1; E:T = ~ 85:15	Oil
13	H	$\underline{i}$-C_3H_7			(E)-CH=CH-	H	Na	D1; E	> 190°C (dec.)
14	CH_3	CH_3			(E)-CH=CH-	H	C_2H_5	E:T = ~ 9:1	Oil
15	CH_3	CH_3			(E)-CH=CH-	H	Na	E	> 160°C (dec.)
16	C_2H_5	C_2H_5			(E)-CH=CH-	H	C_2H_5	E:T = ~ 4:1	Oil
17	C_2H_5	C_2H_5			(E)-CH=CH-	H	Na	E:T = ~ 4:1	> 170°C (dec.)
18	CH_3	CH_3		3,5diCH_3	(E)-CH=CH-	H	C_2H_5	E:T = ~ 9:1	Oil
19	CH_3	CH_3		3,5diCH_3	(E)-CH=CH-	H	Na	E:T = ~ 9:1	> 190°C (dec.)

TABLE II

(Compounds of Group IAb; Ro = ring A)

Cmpd. No.	R	R_1	R_2, R_3	R_4,R_5,R_6	X	R_{10}	Isomers	m.p.
20	H	i-C_3H_7	H	4-F	(E)-CH=CH-	H	Ol; trans	Oil
21	H	i-C_3H_7	↓	4-F	(E)-CH=CH-	H	Ol; cis: trans = ~ 4:1	Oil
22	CH_3	CH_3	↓	4-F	(E)-CH=CH-	H	trans	64°-66°C
23	CH_3	CH_3	↓	3,5diCH_3	(E)-CH=CH-	H	trans : cis = ~ 4:1	Foam

TABLE III

(Compounds of Group IBa; Ro = ring A)

Cmpd. No.	R + R_1	R_2,R_3	R_4,R_5,R_6	X	R_{10}	R_{11}	Isomers	m.p.
1	$(CH_2)_4$	H	4-F	(E)-CH=CH-	H	C_2H_5	E:T = ~24:1	90-93°
2	$(CH_2)_4$	H	4-F	(E)-CH=CH-	H	Na	E:T = ~24:1	> 170° (dec.)
3	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	H	E:T = ~3-9:1	Oil
4	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	Na	E:T = ~3-9:1	> 160° (dec.)
5	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	C_2H_5	E:T = ~3-9:1	Oil
8	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	Na	Erythro	> 170° (dec.)
9	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	Na	Threo	> 160° (dec.)
24	$(CH_2)_2$	H	4-F	(E)-CH=CH-	H	C_2H_5	E:T = ~ 89:11	Oil
25	$(CH_2)_2$	H	4-F	(E)-CH=CH-	H	Na	E:T = ~ 9:1	> 160° (dec.)
26	$(CH_2)_5$	H	4-F	(E)-CH=CH-	H	C_2H_5	E:T = ~ 3:1	Oil
27	$(CH_2)_4$	H	H	(E)-CH=CH-	H	C_2H_5	E:T = ~ 3:1	Oil
28	$(CH_2)_4$	H	4-F	$(CH_2)_2$	H	C_2H_5	E:T = ~ 9:1	Oil

TABLE IV

(Compounds of Group IBb; Ro = ring A)

Cmpd. No.	R + R_1	R_2,R_3	R_4,R_5,R_6	X	R_{10}	Isomers	m.p.
6	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	trans	Solid foam
7	$(CH_2)_4$	H	3,5diCH_3	(E)-CH=CH-	H	cis	Solid foam
30	$(CH_2)_4$	H	4-F	(E)-CH=CH-	H	trans:cis=~3:1	Oil

TABLE V

(Compounds of Group IBa)

Cmpd. No.	R + R_1	R_2,R_3	Ro	X	R_{10}	R_{11}	Isomers	m.p.
29	$(CH_2)_4$	H	i-C_3H_7	(E)-CH=CH-	H	C_2H_5	E:T = ~9:1	Oil

TABLE VI

(Compounds of Group IBc; Ro = ring A)

Cmpd. No.	R + R_1	R_2,R_3	R_4,R_5,R_6	X	R_{10}	R_{11}	Q	Isomers	m.p.
10	$(CH_2)_4$	H	4-F	(E)-CH=CH-	H	C_2H_5	-C- ‖ O	-	107-109°
11	$(CH_2)_4$	H	4-F	(E)-CH=CH-	H	C_2H_5	-C- O O CH_3 CH_3	-	Oil

In Tables I - VI

D1 = approximately 1:1 mixture of diastereoisomers with respect to the 1-position of the indene ring

E = erythro racemate

T = threo racemate

cis = cis lactone

trans = trans lactone

Thus, for example, "D1; E:T =∿85:15" means that the compound is a mixture of eight stereoisomers wherein the ratio of the four erythro stereoisomers to the four threo stereoisomers is about 85:15 and the ratio of the four stereoisomers wherein R_1 has one configuration to the four stereoisomers wherein R_1 has the opposite configuration is about 1:1.

N.M.R. Data

Cmpd.No.

12 ($CDCl_3$): 0.3 (d (J=10 Hz.), 3H), 1.2 (t, 3H), 1.35 (d (J=10 Hz.), 3H), 1.7 (m, 2H), 2.5 (m, 2H), 3.3 (s, 1H), 3.7 (m, 1H), 4.2 (q, 2H), 4.3 (m, 1H), 4.5 (m, 1H), 5.8 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz.), 1H), 7.0-7.5 (m, 8H)

13 ($CDCl_3$+CD_3OD): 0.35 (d (J=10 Hz.), 3H), 1.4 (d (J=10 Hz.), 3H), 1.65 (m, 2H), 2.2-2.6 (m, 3H), 3.75 (bs, 1H), 4.15 (m, 1H), 4.4 (m, 1H), 5.9 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.55 (d (J=20 Hz.), 1H), 7.0-7.5 (m, 8H)

14 ($CDCl_3$): 1.3 (t, 3H), 1.5 (d, 6H), 1.6-1.9 (m, 2H), 2.5 (d, 2H), 4.2 (q, 2H), 4.3 (m, 1H), 4.5 (m, 1H), 6.0 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.55 (d (J=20 Hz.), 1H), 7.1-7.4 (m, 8H)

15 ($CDCl_3$+CD_3OD): 1.4 (d, 6H), 1.5 (m, 2H), 2.2 (m, 2H), 4.15 (m, 1H), 4.3 (m, 1H), 5.9 (dd J_1=10 Hz., J_2=20 Hz.), 1H), 6.4 (d (J=20 Hz.), 1H), 7.0-7.4 (m, 8H)

16 ($CDCl_3$): 0.35 (m, 6H), 1.3 (t (J=10 Hz.), 3H), 1.7 (m, 4H), 2.0 (m, 4H), 2.5 (d (J=10 Hz.), 2H), 4.2 (q (J=10 Hz.), 2H), 4.3 (m, 1H), 4.45 (m, 1H), 5.9 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz.), 1H), 7.1-7.4 (m, 8H)

17 ($CDCl_3$+CD_3OD): 0.35 (m, 6H), 1.7 (m, 2H), 2.0 (m, 4H), 2.3 (m, 2H), 4.1 (m, 1H), 4.35 (m, 1H), 5.9 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz.), 1H), 7.0-7.5 (m, 8H)

Cmpd.No.

18 ($CDCl_3$): 1.25 (t, 3H), 1.5 (d (J=8 Hz.), 6H), 1.55-1.9 (m, 2H), 2.35 (s, 6H), 2.5 (d, 2H), 4.15 (q, 2H), 4.3 (m, 1H), 4.45 (m, 1H), 5.9 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.55 (d (J=20 Hz.), 1H), 7.0-7.4 (m, 7H)

19 ($CDCl_3$+CD_3OD): 1.4 (d, 6H), 1.5-1.9 (m, 2H), 2.2-2.5 (m, 8H), 4.1 (m, 1H), 4.45 (m, 1H), 5.9 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz.), 1H), 7.0-7.4 (m, 7H)

20 ($CDCl_3$): 0.35 (d (J=10 Hz.), 3H), 1.4 (d (J=10 Hz.), 3H), 1.8-2.2 (m, 3H), 2.4-2.9 (m, 3H), 3.8 (bs, 1H), 4.45 (bs, 1H), 5.3 (m, 1H), 5.9 (dq, 1H), 6.6 (d (J=20 Hz.), 1H), 7.0-7.6 (m, 8H)

21 ($CDCl_3$): 0.35 (d (J=10 Hz.), 3H), 1.4 (d (J=10 Hz.), 3H), 1.8-2.2 (m, 2H), 2.25-3.05 (m, 4H), 3.8 (bs, 1H), 4.3 (m, 1H), 4.8 (m, 1H), 5.9 (m, 1H), 6.6 (d (J=20 Hz.), 1H), 7.0-7.6 (m, 8H)

22 ($CDCl_3$): 1.5 (d (J=8 Hz.), 6H), 1.8-2.1 (m, 2H), 2.5-2.8 (m, 2H), 4.4 (m, 1H), 5.2 (m, 1H), 5.9 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.55 (d (J=20 Hz.), 1H), 7.1-7.5 (m, 8H)

23 ($CDCl_3$): 1.5 (d, 6H), 1.8-2.1 (m, 2H), 2.4 (s, 6H), 2.5-3.0 (m, 2H), 4.4 (m, 1H), 5.2 (m, 1H), 5.9 (dd, 1H), 6.6 (d, 1H), 6.95-7.45 (m, 7H)

Cmpd.No.

24 ($CDCl_3$): 1.3 (t, 3H), 1.5-2.0 (m, 6H), 2.5 (d, 2H), 3.2 (s, 1H), 3.8 (s, 1H), 4.2 (q, 2H), 4.2-4.45 (m, 2H), 5.5 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.5 (d (J=20 Hz.), 1H), 7.0-7.45 (m, 8H)

25 ($CDCl_3$+CD_3OD): 1.5-2.4 (m, 8H), 4.1 (m, 1H), 4.3 (m, 1H), 5.5 (dd (J_1=10 Hz., J_2=20 Hz.), 1H), 6.4 (d (J=20 Hz.), 1H), 7.0-7.5 (m, 8H)

26 (C_6D_6) 0.9 (t,J=10 Hz, 3H), 1.1-2.4 (m, 14H), 3.8 (q,J=10 Hz, 2H), 3.9-4.4 (m, 2H), 6.0 (dd, J=20 and 10Hz, 1H), 6.7 (m, 1H) 6.8-7.8 (m, 8H).

27 (C_6D_6) 0.9 (m, 2H), 1.2-2.5 (m, 12H), 3.8 (m, 2H), 4.0 (m, 1H), 4.1-4.3 (m, 1H), 5.9 (dd,J=20 and 10 Hz, 1H), 6.8 (dd,J=20 and 10 Hz, 1H), 6.9-7.5 (m, 9H).

11 (C_6D_6) 0.9 (t,J=10 Hz, 3H), 1.2-3.1 (m, 12H), 3.2 (ds, 6H), 3.9 (q,J=10 Hz, 2H), 4.8 (m, 1H), 6.5 (d,J=20 Hz, 1H), 6.8-7.4 (m, 8H), 7.7 (d,J=20 Hz, 1H).

28 ($CDCl_3$) 1.3 (t, 3H), 1.4-2.5 (m, 16H), 3.7 (m, 2H), 4.2 (q, J=10 Hz, 2H), 6.8-7.3 (m, 8H).

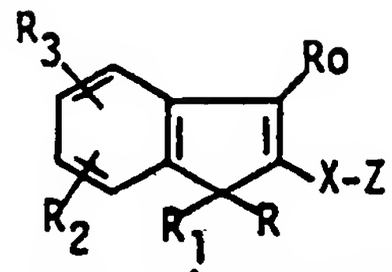
Cmpd.No.		
30	($CDCl_3$)	1.8-3.0 (m, 12H), 4.4 (m, 1H), 5.2 (m, 1H), 5.7 (dd, J=10 and 20 Hz, 1H), 6.5 (d, J=20 Hz, 1H), 7.1-7.5 (m, 8H). The following additional smaller peaks : 4.3 (m), 4.7 (m), 5.8 (dd), 6.45 (d), due to the corresponding cis lactone.
29	(C_6D_6)	0.9 (t, J=10 Hz, 3H), 1.4 (dd, J=10 and 20 Hz, 6H), 1.5-2.4 (m, 12H), 3.4 (m, 1H), 3.8 (q, J=10 Hz, 2H), 4.15 (m, 1H), 4.4 (m, 1H), 5.8 (dd, J=20 and 10 Hz, 1H), 6.9 (dd, J=20 and 1 Hz, 1H), 7.0-7.6 (m, 4H). The following small peaks at 4.55(m), 5.9 (dd), 6.8 (d), due to the threo isomer.

All nuclear magnetic resonance spectra were taken at ambient temperature on a 200 MHz. spectrometer. All chemical shifts are given in p.p.m. (δ) relative to tetramethylsilane, and where a single δ value is given for anything other than a sharp singlet, it is its center point. In the N.M.R. data:

bs = broad singlet
d = doublet
dd = doublet of a doublet
dq = doublet of a quartet
m = multiplet
q = quartet
s = singlet
t = triplet
ds = double singlet

WE CLAIM:

1. A compound of formula I



I

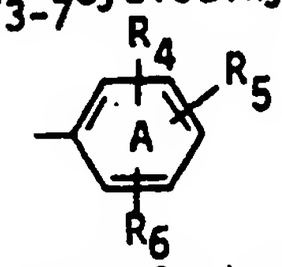
wherein R is hydrogen or primary or secondary C_{1-6}alkyl,

R_1 is primary or secondary C_{1-6}alkyl or

R and R_1 together are $(CH_2)_m$ or (Z)-CH_2-CH=CH-CH_2-

wherein m is 2, 3, 4, 5 or 6,

Ro is C_{1-6}alkyl, C_{3-7}cycloalkyl or ring A



each of R_2 and R_4 is independently hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

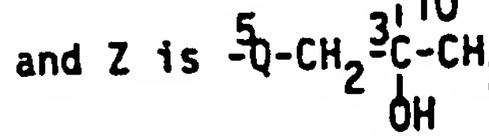
each of R_3 and R_5 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

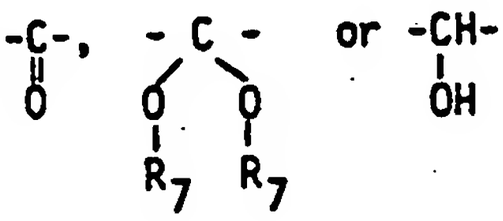
R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

with the proviso that there may only be one each of trifluoromethyl, phenoxy or benzyloxy on each of the phenyl and indene rings

X is $-(CH_2)_n-$ or $-(CH_2)_qCH=CH(CH_2)_q-$

wherein n is 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1,

and Z is  II

wherein Q is 

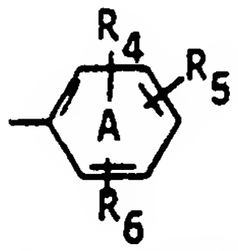
wherein each R_7 is the same primary or secondary C_{1-6}alkyl or together they represent $-(CH_2)_2-$, $-(CH_2)_3-$,

R_{10} is hydrogen or C_{1-3}alkyl,

with the proviso that Q may be other than $-\underset{\underset{OH}{|}}{CH}-$ only when X is -CH=CH- or $-CH_2-CH=CH-$ and/or R_{10} is C_{1-3}alkyl,

in free acid form, or in the form of an ester or δ-lactone thereof or in salt form as appropriate.

2. A compound according to Claim 1 wherein

Ro represents ring A 

R is hydrogen or primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, and

R_1 is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom or

R and R_1 taken together are $-(CH_2)_m-$ or $(Z)-CH_2-CH=CH-CH_2-$, wherein m is 2, 3, 4, 5 or 6,

R_2 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

with the proviso that not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

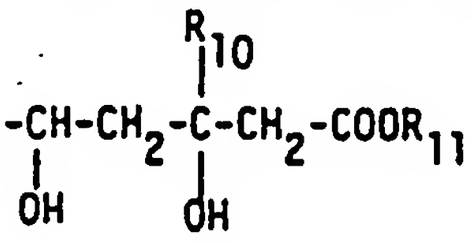
R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

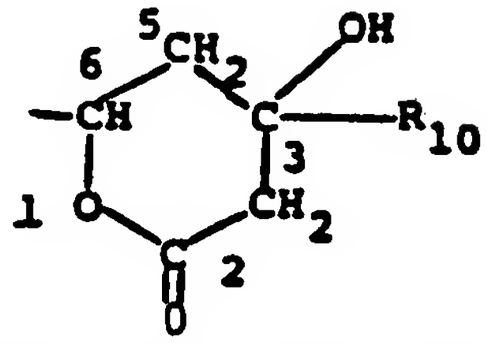
R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_6 is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

with the provisos that not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy, and not more than one of R_4 and R_5 is benzyloxy,

X is $-(CH_2)_n-$ or (E)-CH=CH-,
wherein n is 1, 2 or 3, and

Z is  (a) or

 (b),

wherein R_{10} is hydrogen or C_{1-3}alkyl, and
R_{11} is hydrogen, R_{12} or M,
wherein R_{12} is a physiologically acceptable and hydrolyzable ester group, and
M is a pharmaceutically acceptable cation.

3. A compound according to Claim 1, wherein R, R_1, Ro, R_2 to R_6, X and Z have meanings selected from those hereinbefore defined in groups (i) to (lvi).

4. A compound selected from erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]-hept-6-enoic acid and erythro-(E)-3,5-dihydroxy-7-[3'-(3",5"-dimethylphenyl)-spiro[cyclopentane-1,1'(1H)-inden]-2'-yl]hept-6-enoic acid in free acid or salt form.

5. A compound according to Claim 4 in sodium salt form.

6. A pharmaceutical composition comprising a compound according to Claim 1 as appropriate in free acid form or in the form of a physiologically hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier.

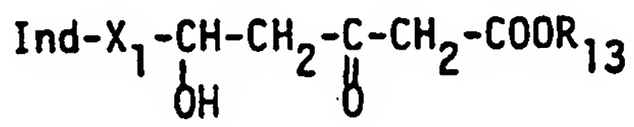
7. A compound according to Claim 1 as appropriate in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use as a pharmaceutical.

8. A compound according to Claim 1 as appropriate in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use in inhibiting cholesterol biosynthesis or treating atherosclerosis.

9. A process for preparing a compound according to Claim 1 which comprises hydrolysing a compound of formula I in ester or lactone form or esterifying or lactonising a compound of formula I in free acid form and when a free carboxyl group is present recovering the compound obtained in free acid form or in the form of a salt.

10. A process for preparing a compound according to Claim 1 which comprises

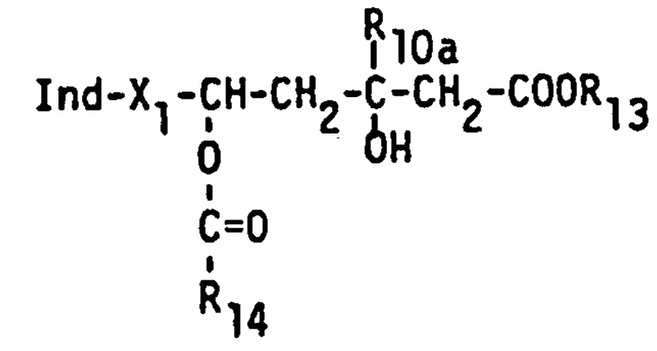
a) when X is $(CH_2)_n$ or (E)-CH=CH- and R_{10} is hydrogen reducing a compound of formula IV



IV

wherein R_{13} is a radical forming an ester, and X_1 is $(CH_2)_n$ or (E)-CH=CH-,

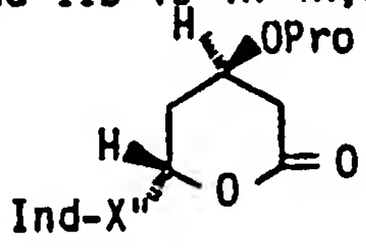
b) when X is $(CH_2)_n$ or (E)-CH=CH- and R_{10} is C_{1-3}alkyl hydrolysing a compound of formula XII



XII

wherein R_{10a} is C_{1-3}alkyl, R_{14} is part of an ester forming group and X_1 and R_{13} are as defined above,

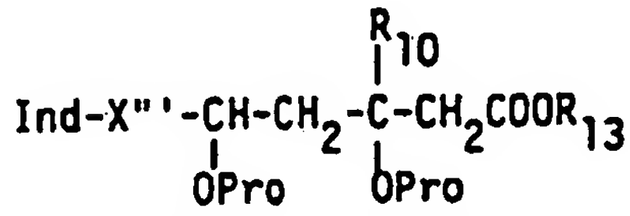
c) when X is -CH=CH- or $-CH_2$-CH=CH- and IIb is in 4R,6S configuration or X is $-CH_2CH_2$ or $CH_2CH_2CH_2$ and IIb is in 4R,6R configuration deprotecting a compound of formula XXXIX



XXXIX

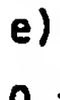
wherein X" represents $-CH_2CH_2$, $-CH_2CH_2CH_2$, -CH=CH- or $-CH_2CH$=CH- and Pro is a protecting group,

d) when X is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_qCH=CH(CH_2)_q-$ deprotecting a compound of formula XXXII



XXXII

wherein X"' is $-(CH_2)_2-$, $-(CH_2)_3-$ or $-(CH_2)_q-CH=CH-(CH_2)_q-$, and q, R_{10}, R_{13} and Pro are as defined above,

e) when Q is  oxidising the corresponding compound of formula I wherein Q is 

f) when Q is  and II is in ester form ketalising the corresponding compound of formula I wherein Q is 

g) hydrolysing a compound of formula I in the form of an ester or a lactone or

h) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free acid form or in the form of a salt.

11. A compound of formulae IV, XII, XXXII, XXXIV, XXXVII, XXXIX, XLVI, XLVIII, L-LII, LV, LVII-LIX, LX, LXI, LXIV.

12. A compound according to Claim 1 or a process according to Claim 10 substantially as hereinbefore described with reference to Examples 1 to 7 and/or compounds 1 to 30.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 85/00653

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 C 69/738; C 07 C 69/732; C 07 C 59/90; C 07 C 59/56; C 07 C 59/34; C 07 D 309/30; A 61 K 31/365; A 61 K 31/22; ./.

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC[4]	C 07 C 69 C 07 C 59 A 61 K 31 C 07 D 309

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0114027 (SANDOZ) 25 July 1984, see the whole document; pages 20-22; examples 1-10; page 30, line 4 - page 34 (cited in the application)	1-3,6-10
A	EP, A, 0117228 (SANDOZ) 29 August 1984, see whole document; pages 21-24; page 35, line 11 - page 39; examples 1-18 (cited in the application)	1-3,6-10
A	EP, A, 0113881 (MERCK) 25 July 1984, see page 9, line 28 - page 10; examples 1-10; claims	1-3,6-9
A	EP, A,0011928 (SANKYO) 11 June 1980, see page 10, line 18 - page 15; examples; claims	1-3,6-9
P,A	Journal of Medicinal Chemistry, volume 28, no. 43, March 1985, Columbus, Ohio, (US) G.E. Stokker et al.:"3-hydroxy-3-methyl-glutaryl-coenzyme a reductase inhibitors. 1. Structural modification of 5-Substituted 3,5-dihydroxypentanoic adics and	./.

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
	11 JUIN 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	L. ROSSI

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 85/00653

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/19

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
	their lactone derivatives", pages 347-358, see page 347; page 349, biological effects; page 351, table III, compound 56; pages 352-353	1-3,6-10

---

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th March 1986	11 JUIN 1986
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	L. ROSSI

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..... because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers ....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

- 1-10,11 (partially): Compounds of formula I, their preparation, their intermediates and their application (claim 11, compounds of formulas IV,XII,XXXII,XXXIV)
- 11 (partially) : Intermediates of formulas XXXVII,XXXIX,XLVIII, L-LII,LV,LVII-LIX,LX,LXI,LXIV

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: 1-10,11 (partially)

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 85/00653 (SA 11507)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/06/86

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0114027	25/07/84	WO-A- 8402131	07/06/84
		AU-A- 2261283	18/06/84
		JP-T- 60500015	10/01/85
EP-A- 0117228	29/08/84	WO-A- 8402903	02/08/84
		AU-A- 2433184	15/08/84
		JP-T- 60500499	11/04/85
EP-A- 0113881	25/07/84	JP-A- 59130249	26/07/84
		US-A- 4472426	18/09/84
		US-A- 4503072	05/03/85
EP-A- 0011928	11/06/80	US-A- 4248889	03/02/81
		JP-A- 55059140	02/05/80
		AT-T- 910	15/05/82